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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,184	08/31/2006	Pierre J-M. Riviere	052209-0150	6577

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,184	RIVIERE ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060725*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) filed 25 July 2006 has been entered.

Election/Restrictions

Applicant's election, with traverse, of Group I, claims 1-12, in the reply filed on 28 May 2008 is acknowledged.

Applicant traverses the Requirement for Restriction/Election on the ground(s) that the Office Action does not establish that the claims lack a common technical feature. Specifically, Applicant argues that U.S. Patent No: 6,316,410 does not mention bone cancer or bone originated cancer.

Applicant's arguments have been fully considered but have not been found to be persuasive.

Claim 1 in Group I is directed to a method of ameliorating symptoms associated with the growth of bone-metastasized cancer or bone-originated cancer, comprising administering to an individual in need thereof a medicament comprising an amount of PTH receptor agonist to reduce bone loss, bone fracturing, and/or reduce pain. Barbier et al. (U. S. Patent No: 6,316,410 B1, issued on 13 November 2001) teaches the use of PTH analogues, e.g., hPTH-(1-34), for treating osteoporosis (col. 2, lines 26-34). Barbier et al. teaches that osteoporosis is characterized by the reduction of total bone mass and increased bone fragility, and often results in spontaneous fractures of load-

bearing bones (col. 1, lines 16-36). These are the same symptoms as those associated with the growth of bone-metastasized cancer or bone-originated cancer, for example, Applicant describes that "symptoms associated with the growth of bone-metastasized cancer or bone-originated cancer, such as bone loss, bone fracturing, and pain" (see Abstract). Therefore, the teaching of the '410 patent meets the limitations of claim 1. Thus the technical feature of Group I lacks novelty or inventive step and does not make a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-20 are pending. Claims 13-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1-12 are under examination.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The specification does not contain as a first paragraph, a claim to benefit of priority to any application. Upon review of the declaration, it would appear that applicant is claiming benefit of priority to a provisional application 60/538,512.

The title "Novel Use" at the top of the first page of the specification is inconsistent to the Application Data Sheet.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 5-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of ameliorating symptoms associated with the growth of bone-metastasized cancer or bone-originated cancer, comprising administering to an individual in need thereof a medicament comprising an effective amount of a PTH receptor agonist, which is a human parathyroid hormone PTH(1-84), human PTH(1-34), or an analogue thereof, to reduce bone loss, bone fracturing, and/or reduce pain,

does not reasonably provide enablement for the genus of PTH receptor agonists as currently claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are directed to a method of ameliorating symptoms associated with the growth of bone-metastasized cancer or bone-originated cancer, comprising administering to an individual in need thereof a medicament comprising an amount of a PTH receptor agonist effective to reduce bone loss, bone fracturing, and/or reduce pain; wherein the PTH receptor agonist is a parathyroid hormone (PTH) or an analogue thereof, a parathyroid hormone-related protein (PTHrP) or an analogue thereof, wherein said amount is effective to reduce pain, is from 0.1-1000 μg, or 20-200 μg. The claims are broad in that they encompass and require the use of a large genus of molecules, i.e., PTH receptor agonists. While Applicant defines the genus as "PTH peptides and peptide analogues, and PTHrP peptides and peptide analogues, that bind and activate the PTH receptor "(pp. 5, lines 2-4), and further describes a representative number of

species for these peptides and peptide analogues (pp. 8, Table 2; pp. 9, Table 3), Applicant, however, has not provided guidance and sufficient support to use the genus of PTH receptor agonists for ameliorating symptoms associated with the growth of bone-metastasized cancer or bone-originated cancer, including reducing pain. All that have been provided are using human PTH(1-34), which shares an agonistic activity as human PTH(1-84). While the prior art (Barbier et al., U. S. Patent No: 6,316,410 B1, reference provided previously) teaches the use of PTH analogues for treating osteoporosis, Barbier et al., however, does not teach that the PTH analogues can be used to reduce bone cancer-associated pain. Rabbani et al. (Biochem., 1990, 29:10080-10089) studied function and bioactivities for hPTH analogues, and found that peptide analogues vary dramatically in bioactivity, for example, fMet-hProPTH displayed 10% of the *in vitro* activity of hPTH-(1-84) and was a partial agonist *in vivo* (see Abstract). Further, Yin et al. (J. Clin. Invest., 1999, 103(2):197-206) teaches a positive correlation of PTHrP produced by breast cancer cells with enhanced osteolytic bone metastasis, and decreased survival (see Abstract). Yin et al. states that "PTHrP is a tumor product that stimulates osteoclastic bone resorption and renal tubular re-absorption of calcium by binding to a common PTH/ PTHrP receptor. The majority of patients with solid tumors and hypercalcemia have increased plasma PTHrP concentrations" (pp. 197, col. 2, 1st full paragraph). Therefore, the art teaches that it is desirable to reduce the amount of PTHrP, which is in contradiction to the instantly claimed invention.

Since the specification fails to provide sufficient guidance for ameliorating symptoms, e.g., cancer pain, associated with the growth of bone-metastasized cancer or bone-originated cancer, by using the genus of PTH receptor agonists recited in the claims, the skilled artisan would need to pick up one of the agonist and determine their usefulness in a clinical setting. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to determine whether the claimed genus of PTH receptor agonists can be used for ameliorating symptoms associated with the growth of bone-metastasized cancer or bone-originated cancer, the lack of direction/guidance presented in the specification, the absence of working examples directed to same, the complex nature of the invention, the state of the art which teaches that different PTH analogues exhibit different *in vivo* activity, and that an increase in PTHrP is correlated with an increased osteolytic bone metastasis and decreased survival, and the breadth of the claim which encompasses the use of the genus of PTH receptor agonists, including PTHrP and analogues thereof, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 7 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Hock (WO 01/21198, International Publication Date 29 March 2001).

The claims are directed to a method of ameliorating symptoms associated with the growth of bone metastasized cancer or bone-originated cancer, comprising administering to an individual in need thereof a medicament comprising an amount of PTH receptor agonist effective to reduce bone loss, bone fracturing, and/or pain (claim 1); wherein said amount is effective to reduce pain, is from 0.1-1000 μg, and is from 20-200 μg (claims 2, 10, 11); wherein said PTH receptor agonist is PTH or an analogue thereof, which is PTH (1-34) or teriparatide acetate (claims 3, 4, 12); and wherein said individual has bone metastasized cancer, originated from breast cancer, prostate cancer, lung cancer, kidney cancer, thyroid cancer or myeloma (claims 6, 7).

Hock teaches a method for reducing the risk of cancer in a subject by administering a parathyroid hormone, such as rhPTH(1-34) (pp. 6, lines 1-2, and lines 20-22). Please note that teriparatide is rhPTH(1-34) (see abstract in Orwoll et al., 2003, J. Bone Miner. Res., 18(1):9-17). Hock teaches that the hormone is administered in a daily dose in the range of at least about 15-40 μg (pp. 6, lines 22-23). Hock teaches that certain cancers, such as breast, prostate and lung cancer, can spread to bone, and that the method can ameliorate the damage from metastasis to bone, particularly when the spread to bone has caused a significant defect in the bone (pp. 8, lines 15-17). Hock teaches that the method can aid maintenance and rebuilding of the bone in a cancer

patient undergoing or at risk of metastasis or other growth of a tumor in bone, and can reduce the risk of fracture in such bone (pp. 8, lines 19-30).

While Hock does not expressly teach the amount to be effective to reduce pain, this limitation would reasonably be considered to be inherent since exactly the same dosage of parathyroid hormone is administered into the same patient population for the same purpose, e.g., ameliorating the damage from metastasis or tumor-growth in bone, and reducing the risk of fracture in such bone. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), as are their processes and yields (**In re Von Schickh**, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hock (WO 01/21198), in view of McKenna et al. (J. Bone Joint Surg. Am., 1966, 48:1-26).

The disclosure of Hock is as set forth above. Hock, however, does not teach that the individual has bone-originated cancer, e.g., sarcoma (claims 8, 9).

McKenna et al. analyzed sarcomas of osteogenic series in 552 cases with primary or secondary osteogenic sarcoma, and found that the symptoms of the bone

cancer in these patients include pathological fracture and pain (pp. 8, section "Signs and Symptoms").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hock, with those of McKenna et al., to use a parathyroid hormone to ameliorate the damage resulted from the growth of a primary osteosarcoma. One of ordinary skill in the art would have been motivated to do so, because Hock teaches that administration of a parathyroid hormone can ameliorate the damage caused by bone metastasized cancer, can aid maintenance and rebuilding of the bone, and reduce the risk of fracture in such bone, and McKenna et al. further teaches that the symptoms for both primary and secondary osteosarcoma are similar, i.e., patients develop pathological fracture and pain. Therefore, the combined teachings provide a reasonable expectation of successfully ameliorating the damage in these patients.

Claim Objections

Claims 1, 3-5, 7 and 10-12 are objected to because of the following informalities:

Claims 1, 3-5 and 10-12 use acronyms without first defining what they represent in the independent claims (for example, "PTH"). While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

In claim 1, the word "a" should be added before "PTH receptor agonist".

In claim 7, the word "or" before "thyroid cancer" should be deleted.

Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Christine J Saoud/
Primary Examiner, Art Unit 1647

Xiaozhen Xie, Ph.D.
August 12, 2008